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Efficient Copper-Catalyzed S-Vinylation of Thiols with Vinyl Halides

Hsin-Lun Kao and Chin-Fa Lee*

Department of Chemistry, National Chung Hsing University, Taichung, Taiwan 402, R.O.C

cfalee@dragon.nchu.edu.tw

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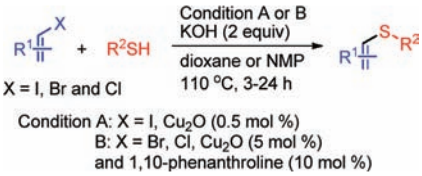
ABSTRACT



The synthesis of vinyl sulfides through the coupling reaction of thiols with vinyl iodides, bromides, and chlorides is described. The thiols can couple with aryl iodides in the presence of only 0.5 mol % Cu_2O without the need for an ancillary ligand. In the presence of 5 mol % of Cu_2O and 10 mol % 1,10-phenanthroline as the ligand, the more challenging alkyl vinyl bromides can also be coupled with thiols, giving the vinyl sulfides in good to excellent yields.

Vinyl sulfides are important building blocks in organic synthesis[1] and are present in many biologically active compounds.[2] Many approaches for preparing vinyl sulfides are known;[3] for example, the addition of thiols to alkynes is one of the methods to construct vinyl sulfides. However, this method suffers from the issue of regioselectivity, leading to the formation of undesired regioisomers.[4] The transition-metal-catalyzed cross-coupling of the C–S bond provides an attractive route to the preparation of

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(1) (a) Sader, H. S.; Johnson, D. M.; Jones, R. N. *Antimicrob. Agents Chemother.* **2004**, *48*, 53. (b) Ceruti, M.; Balliano, G.; Rocco, F.; Milla, P.; Arpicco, S.; Cattel, L.; Viola, F. *Lipids* **2001**, *36*, 629. (c) Marcantoni, E.; Massaccesi, M.; Petrini, M.; Bartoli, G.; Bellucci, M. C.; Bosco, M.; Sambri, L. *J. Org. Chem.* **2000**, *65*, 4553.

(2) (a) Xu, H.-J.; Zhao, X.-Y.; Feng, Y.-S.; Deng, J.; Fu, Y. *Synlett* **2008**, *19*, 3063. (b) Reddy, V. P.; Kumar, A. V.; Swapna, K.; Rao, K. R. *Org. Lett.* **2009**, *11*, 1697. (c) Litaudon, M.; Trigalo, F.; Martin, M.-T.; Frappier, F.; Guyot, M. *Tetrahedron* **1994**, *50*, 5323. (d) Lee, A. H. F.; Chen, J.; Liu, D.; Leung, T. Y. C.; Chan, A. S. C.; Li, T. *J. Am. Chem. Soc.* **2002**, *124*, 13972. (e) Freydank, A. C.; Humphrey, M. G.; Friedrich, R. W.; Luther-Davies, B. *Tetrahedron* **2002**, *58*, 1425. (f) Zhang, H.; Cao, W.; Ma, D. *Synth. Commun.* **2007**, *37*, 25. (g) Heynderickx, A.; Samat, A.; Guglielmetti, R. *Synthesis* **2002**, 1747.

(3) For reviews on transition-metal-catalyzed C–S coupling reactions, see: (a) Beletskaya, I. P.; Ananikov, V. P. *Chem. Rev.* **2011**, *111*, 1596. (b) Eichman, C. C.; Stambuli, J. P. *Molecules* **2011**, *16*, 590. (c) Beletskaya, I. P.; Ananikov, V. P. *Eur. J. Org. Chem.* **2007**, 3431. (d) Ley, S. V.; Thomas, A. W. *Angew. Chem., Int. Ed.* **2003**, *43*, 5400. (e) Procter, D. J. *J. Chem. Soc., Perkin Trans. 1* **2001**, 335. (f) Kondo, T.; Mitsudo, T.-a. *Chem. Rev.* **2000**, *100*, 3205. (g) Lindley, J. *Tetrahedron* **1984**, *40*, 1433.

(4) (a) Sugoh, K.; Kuniyasu, H.; Sugae, T.; Ohtaka, A.; Takai, Y.; Tanaka, A.; Machino, C.; Kambe, N.; Kurosawa, H. *J. Am. Chem. Soc.* **2001**, *123*, 5108. (b) Ogawa, A.; Ikeda, T.; Kimura, K.; Hirao, T. *J. Am. Chem. Soc.* **1999**, *121*, 5108. (c) Backvall, J. E.; Ericsson, A. *J. Org. Chem.* **1994**, *59*, 5850. (d) Kuniyasu, H.; Ogawa, A.; Sato, K. I.; Ryu, I.; Kambe, N.; Sonoda, N. *J. Am. Chem. Soc.* **1992**, *114*, 5902.

(5) For selected examples on palladium-catalyzed coupling reaction of aryl halides with thiols, see: (a) Itoh, T.; Mase, T. *Org. Lett.* **2004**, *6*, 4587. (b) Mispelaere-Canivet, C.; Spindler, J.-F.; Perrio, S.; Beslin, P. *Tetrahedron* **2005**, *61*, 5253. (c) Fernández-Rodríguez, M. A.; Shen, Q.; Hartwig, J. F. *J. Am. Chem. Soc.* **2006**, *128*, 2180. (d) Alvaro, E.; Hartwig, J. F. *J. Am. Chem. Soc.* **2009**, *131*, 7858. (e) Fernández-Rodríguez, M. A.; Hartwig, J. F. *Chem.—Eur. J.* **2010**, *16*, 2355. (f) Zeng, F.-L.; Alper, H. *Org. Lett.* **2010**, *12*, 5567.

(6) For examples on nickel-catalyzed coupling reaction of aryl halides with thiols, see: (a) Percec, V.; Bae, J.-Y.; Hill, D. H. *J. Org. Chem.* **1995**, *60*, 6895. (b) Zhang, Y.; Ngeow, K. N.; Ying, J. Y. *Org. Lett.* **2007**, *9*, 3495.

(7) For examples on iron-catalyzed coupling reaction of aryl halides with thiols, see: (a) Wu, J.-R.; Lin, C.-H.; Lee, C.-F. *Chem. Commun.* **2009**, 4450. (b) Wu, W.-Y.; Wang, J.-C.; Tsai, F.-Y. *Green Chem.* **2009**, *11*, 326. (c) Qiu, J.-W.; Zhang, X.-G.; Tang, R.-Y.; Zhong, P.; Lia, J.-H. *Adv. Synth. Catal.* **2009**, *351*, 2319. (d) Correa, A.; Carril, M.; Bolm, C. *Angew. Chem., Int. Ed.* **2008**, *47*, 2880.

(8) For indium-catalyzed coupling reaction of aryl halides with thiols, see: Reddy, V. P.; Swapna, K.; Kumar, A. V.; Rao, K. R. *J. Org. Chem.* **2009**, *74*, 3189.

(9) For cobalt-catalyzed coupling reaction of aryl halides with thiols, see: Wong, Y.-C.; Jayanth, T. T.; Cheng, C.-H. *Org. Lett.* **2006**, *8*, 5613.

(10) For examples on copper-catalyzed coupling reaction of aryl halides with thiols, see: (a) Herradura, P. S.; Pendola, K. A.; Guy, R. K. *Org. Lett.* **2000**, *2*, 2019. (b) Kwong, F. Y.; Buchwald, S. L. *Org. Lett.* **2002**, *4*, 3517. (c) Savarin, C.; Srogl, J.; Liebeskind, L. S. *Org. Lett.* **2002**, *4*, 4309. (d) Bates, C. G.; Gujadhur, R. K.; Venkataraman, D. *Org. Lett.* **2002**, *4*, 2803. (e) Zhu, D.; Xu, L.; Wu, F.; Wan, B. S. *Tetrahedron Lett.* **2006**, *47*, 5781. (f) Lv, X.; Bao, W. *J. Org. Chem.* **2007**, *72*, 3863. (g) Carril, M.; SanMartin, R.; Domínguez, E.; Tellitu, I. *Chem.—Eur. J.* **2007**, *13*, 5100. (h) Verma, A. K.; Singh, J.; Chaudhary, R. *Tetrahedron Lett.* **2007**, *48*, 7199. (i) Buchwald, S. L.; Bolm, C. *Angew. Chem., Int. Ed.* **2009**, *48*, 5586. (j) Larsson, P.-F.; Correa, A.; Carril, M.; Norrby, P.-O.; Bolm, C. *Angew. Chem., Int. Ed.* **2009**, *48*, 5691. (k) Chen, C.-K.; Chen, Y.-W.; Lin, C.-H.; Lin, H.-P.; Lee, C.-F. *Chem. Commun.* **2010**, *46*, 282. (l) Kao, H.-L.; Chen, C.-K.; Wang, Y.-J.; Lee, C.-F. *Eur. J. Org. Chem.* **2011**, 1776. (m) Sahoo, S. K.; Jamir, L.; Guin, S.; Patel, B. K. *Adv. Synth. Catal.* **2010**, *352*, 2538.

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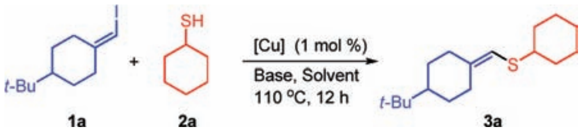
aryl thioethers[5−10] and vinyl sulfides.[11−14] Much attention has been devoted to the coupling reaction of thiols with aryl halides to afford aryl thioethers.[5−10] Conversely, research in the field for the coupling of thiols with vinyl halides has lagged behind. Cobalt,[9] palladium,[11] and copper[12−14] have been reported for the coupling reaction of vinyl halides with thiols in the presence of appropriate ligands. Copper is the cheapest metal among these metal sources for vinyl sulfide synthesis.[12−14] However, the combination of at least 5 mol % of copper salts with suitable ligands is necessary for reacting thiols with vinyl iodides[12] and vinyl bromides.[13] It is important to mention that vinyl bromides are less reactive than vinyl iodides. Interestingly, the vinyl bromides used for copper-catalyzed S-vinylation are limited to 1-(2-bromovinyl)benzene derivatives.[12d,13a,15] Despite the intramolecular S-vinylation of alkyl vinyl bromides catalyzed by copper being known,[14a] the intermolecular copper-catalyzed coupling of thiols with alkyl vinyl bromides is not well-documented. Therefore, the development of a general method to synthesize vinyl sulfides from thiols and vinyl halides is of particular interest. Here we report that the commercially available Cu_2O is reactive toward the coupling of thiols not only with vinyl iodides but also with the more challenging alkyl vinyl bromides under ligand-free conditions. Surprisingly, we discovered that the thiols could react with 1-(2-bromovinyl)benzene and 1-(2-chlorovinyl)benzene without any catalyst; an addition−elimination pathway is suggested for these particular cases.[16] Moreover, with 5 mol % of Cu_2O and 10 mol % of 1,10-phenanthroline[12b,17] as the ligand, the more challenging alkyl vinyl bromides can be coupled with thiols, yielding the vinyl sulfides in good to excellent yields.

In order to determine the optimized conditions, 1-*tert*-butyl-4-(iodomethylene)cyclohexane and cyclohexanethiol were studied and the results are shown in Table 1. We first studied different solvents (Table 1, entries 1−6); the results show that dioxane is the most suitable.[10l] A screen of bases (Table 1, entries 7−16) suggested that strong bases like KOH and KO*t*Bu and weak bases such as K_3PO_4 and Cs_2CO_3 are all suitable for this reaction. The screening of the effect of the copper source (Table 1, entries 17−20) revealed that CuI is the best; however, from a cost point of view, we decided to use Cu_2O as the copper source in combination with KOH as the base for further studies. Control experiments show that a low yield was obtained in the absence of the catalyst (Table 1, entry 21).

Table 1. Optimization of Cu_2O-Catalyzed Coupling Reaction of 1-*tert*-Butyl-4-(iodomethylene)cyclohexane with Cyclohexanethiol[a]



entry	[Cu]	base	solvent	yield (%)[b]
1	Cu_2O	KOH	DMSO	26
2	Cu_2O	KOH	DMF	45
3	Cu_2O	KOH	DME	84
4	Cu_2O	KOH	H_2O	trace
5	Cu_2O	KOH	NMP	71
6	Cu_2O	KOH	dioxane	90
7	Cu_2O	KOEt	dioxane	81
8	Cu_2O	KOMe	dioxane	52
9	Cu_2O	KO*t*-Bu	dioxane	45
10	Cu_2O	NaO*t*-Bu	dioxane	97
11	Cu_2O	NaOH	dioxane	77
12	Cu_2O	K_3PO_4	dioxane	91
13	Cu_2O	K_2CO_3	dioxane	56
14	Cu_2O	Na_2CO_3	dioxane	trace
15	Cu_2O	Cs_2CO_3	dioxane	88
16	Cu_2O	Et_3N	dioxane	27
17	CuI	KOH	dioxane	99
18	CuCl	KOH	dioxane	87
19	CuBr	KOH	dioxane	86
20	CuO	KOH	dioxane	79
21	−	KOH	dioxane	38

[a] Reaction conditions unless otherwise stated: Cu_2O (0.0025 mmol, 0.5 mol %); for CuI, CuCl and CuO (0.005 mmol, 1 mol %), cyclohexanethiol (0.5 mmol), 1-*tert*-butyl-4-(iodomethylene)cyclohexane (0.6 mmol), base (1 mmol), in solvent (0.25 mL). [b] Isolated yields.

As illustrated in Table 2, a variety of vinyl iodides were coupled smoothly with alkyl thiols (Table 2, entries 1−11) and aryl thiols which contain electron-donating or -withdrawing groups (Table 2, entries 12−18), giving the vinyl sulfides in good to excellent yields. Typically, the stereoselectivity was retained in most cases, giving the products **3f**−**3h** and **3s** in good yields with good stereoselectivity (Table 2, entries 5−7 and 18).

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(11) For examples on palladium-catalyzed S-vinylation of vinyl halides, see: (a) Moreau, X.; Campagne, J.-M. *J. Organomet. Chem.* **2003**, *687*, 322. (b) Trostyanskaya, I. G.; Titskiy, D. Y.; Anufrieva, E. A.; Borisenko, A. A.; Kazankova, M. A.; Beletskaya, I. P. *Russ. Chem. Bull.* **2001**, *50*, 2095. (c) Bryan, C. S.; Braunger, J. A.; Lautens, M. *Angew. Chem., Int. Ed.* **2009**, *48*, 7064. (d) Murahashi, S.-I.; Yamamura, M.; Yanagisawa, K.-i.; Mita, N.; Kondo, K. *J. Org. Chem.* **1979**, *44*, 2408.

(12) For examples on copper-catalyzed S-vinylation of vinyl iodides, see: (a) Jiang, B.; Tian, H.; Huang, A.-G.; Xu, M. *Org. Lett.* **2008**, *10*, 2737. (b) Kabir, M. S.; Linn, M. L. V.; Monte, A.; Cook, J. M. *Org. Lett.* **2008**, *10*, 3363. (c) Bates, C. G.; Saejueng, P.; Doherty, M. Q.; Venkataraman, D. *Org. Lett.* **2004**, *6*, 5005. (d) Kabir, M. S.; Lorenz, M.; Van Linn, M. L.; Namjoshi, O. A.; Ara, S.; Cook, J. M. *J. Org. Chem.* **2010**, *75*, 3626. (e) You, W.; Yan, X.; Liao, Q.; Xi, C. *Org. Lett.* **2010**, *12*, 3930.

(13) For examples on copper-catalyzed S-vinylation of vinyl bromides, see: (a) Zheng, Y.; Du, X.; Bao, W. *Tetrahedron Lett.* **2006**, *47*, 1217. (b) Wan, Z.; Jones, C. D.; Koenig, T. M.; Pu, Y. J.; Mitchell, D. *Tetrahedron Lett.* **2003**, *44*, 8257.

(14) For examples on intramolecular copper-catalyzed S-vinylation of vinyl bromides and vinyl chlorides, see: (a) Zhao, Q.; Li, L.; Fang, Y.; Sun, D.; Li, C. *J. Org. Chem.* **2009**, *74*, 459. (b) Sperotto, E.; van Klink, G. P. M.; de Vries, J. G.; van Koten, G. *J. Org. Chem.* **2008**, *73*, 5625.

(15) (a) Liu, Y.; Bao, W. *Tetrahedron Lett.* **2007**, *48*, 4785. (b) Murahashi, S.; Yamamura, M.; Yanagisawa, K.; Mita, N.; Kondo, K. *J. Org. Chem.* **1979**, *44*, 2408. (c) Annunziata, A.; Galli, C.; Gentili, P.; Guarnieri, A.; Beit-Yannai, M.; Rappoport, Z. *Eur. J. Org. Chem.* **2002**, 2136.

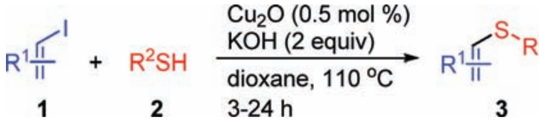
(16) (a) Yamada, S.; Nova, M.; Konno, T.; Ishihara, T.; Yamanaka, H. *Org. Lett.* **2006**, *8*, 843. (b) Huang, X.-H.; He, P.-Y.; Shi, G.-Q. *J. Org. Chem.* **2000**, *65*, 627.

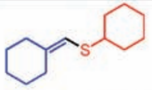
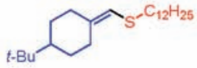
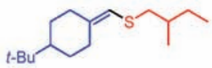
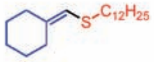
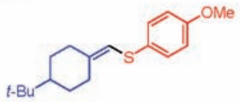
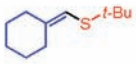
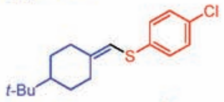
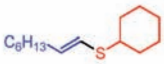
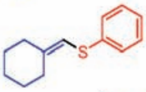
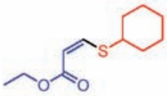
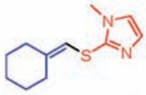
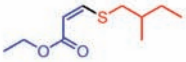
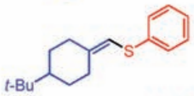
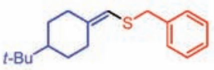
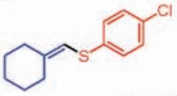
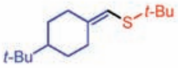
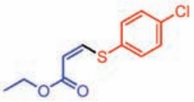
(17) Bates, C. G.; Saejueng, P.; Doherty, M. Q.; Venkataraman, D. *Org. Lett.* **2004**, *6*, 5005.

As mentioned earlier, examples of the coupling reaction of vinyl bromides and chlorides with thiols in the literatures is limited to 1-(2-bromovinyl)benzene and 1-(2-chlorovinyl)benzene derivatives.[12d,13a] However, lower product yields were observed when 1-(2-bromovinyl)-benzene and 1-(2-chlorovinyl)benzene were used instead of vinyl iodides (not shown). To our delight, an excellent yield was obtained when the solvent system was changed from dioxane to NMP;[15] the product **5a** can be obtained in 99% yield (Table 3, entry 1). Surprisingly, this product can also be afforded with 90 and 99% isolated yields through the coupling reaction of 1-dodecanethiol with 1-(2-bromovinyl)benzene or 1-(2-chlorovinyl)benzene *in the absence of any catalyst* (Table 3, entries 2 and 4, respectively)! Thiophenol also worked smoothly with 1-(2-bromovinyl)benzene and 1-(2-chlorovinyl)benzene to provide **5b** with 85 and 94% yields (Table 3, entries 3 and 5, respectively). An addition–elimination pathway is suggested for these particular cases (Scheme S1, see Supporting Information).[16]

We next turned our attention to the more challenging alkyl vinyl bromides and chlorides. The results are shown in Table 4. Only a trace amount of product was detected by GC-MS in the presence of 5 mol % of Cu_2O (Table 4, entry 1). To our delight, a 93% isolated yield of **3d** can be obtained in the presence of 5 mol % Cu_2O and 10 mol % of 1,10-phenanthroline as the ligand. Other ligands such as DMEDA, TMEDA, xantphos, BINAP, and DPEphos have been used for the metal-catalyzed cross-coupling reaction of thiols with aryl halides; however, these ligands could not give us satisfying results (see Supporting Information for details). Based on this promising result for alkyl

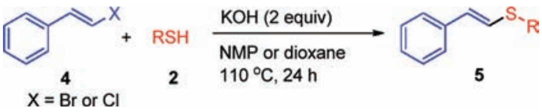
Table 2. Cu_2O-Catalyzed Coupling Reaction of Vinyl Iodides with Thiols[a]

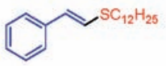
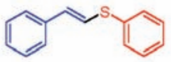
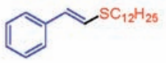


entry	product		yield (%)[b]	entry	product		yield (%)[b]
1		**3b**	91	10		**3k**	84
2		**3c**	73[c]	11		**3l**	78
3		**3d**	91	12		**3m**	96
4		**3e**	67[d]	13		**3n**	97
5		**3f**	92[e]	14		**3o**	90
6		**3g**	82[f]	15		**3p**	86
7		**3h**	79[g]	16		**3q**	88
8		**3i**	67[c]	17		**3r**	85
9		**3j**	70[h]	18		**3s**	88[i]

[a] Reaction conditions unless otherwise stated: Cu_2O (0.0025 mmol, 0.5 mol %), vinyl iodide (0.6 mmol), thiol (0.5 mmol), KOH (1 mmol), in dioxane (0.25 mL) for 12 h; the *trans*/*cis* ratios were determined by GC-MS and ^1H NMR techniques. [b] Isolated yield. [c] 24 h. [d] 36 h. [e] *Trans*/*cis* = 24:1 (starting material) to 22:1 (**3f**). [f] 9 h, *Trans*/*cis* = 1:49 (starting material) to 1:7.6 (**3g**). [g] 3 h, *trans*:*cis* = 1:49 (starting material) to 1:5.5 (**3h**). [h] 48 h. [i] 6 h, *trans*/*cis* = 1:49 (starting material) to 1:8 (**3s**).

Table 3. Cross-Coupling Reaction of 1-(2-Bromovinyl)benzene and 1-(2-Chlorovinyl)benzene with Thiols[a]



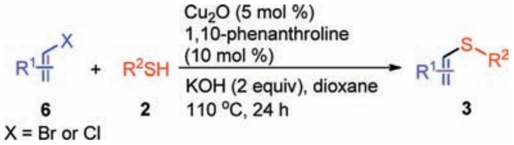
entry	X	product		yield (%)[b]	ratio (*trans*:*cis*)[c]
1	Br		**5a**	99[d]	5:1
2				90	9:1
3	Br		**5b**	85	6:1
4	Cl		**5a**	99	10:1
5	Cl		**5b**	94	6:1

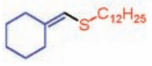
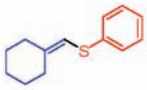
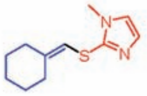
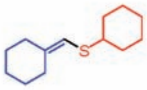
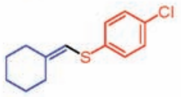
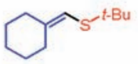
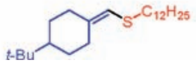
[a] Reaction conditions for vinyl bromide: vinyl bromide (0.6 mmol), thiol (0.5 mmol), KOH (1.0 mmol), in dioxane (0.25 mL); for vinyl chloride: vinyl chloride (0.6 mmol), thiol (0.5 mmol), KOH (1 mmol), in NMP (0.5 mL). [b] Isolated yield. [c] The ratios were determined by GC-MS and ^{1}H NMR techniques. [d] With Cu$_2$O (0.0025 mmol, 0.5 mol %) as a catalyst.

vinyl bromides, we then utilized other alkyl vinyl bromides to couple with thiols; alkyl thiols and thiophenol derivatives are all suitable as coupling partners, giving the corresponding vinyl sulfides in good to excellent yields in general. A trace amount of **3p** was detected when nitrogen-containing thiol was applied (Table 4, entry 5), and **3e** was isolated in only 27% yield when 2-methylpropane-2-thiol was used (Table 4, entry 8). Unfortunately, no product was detected when alkyl vinyl chloride was used as the coupling partner (Table 4, entry 9).

In conclusion, we have demonstrated that commercially available Cu$_2$O is a suitable catalyst for the coupling reaction of vinyl iodides with thiols. 1-(2-Bromovinyl)-benzene and 1-(2-chlorovinyl)benzene could couple smoothly with thiols in the absence of any catalyst. For more challenging alkyl vinyl bromides, we found that the vinyl sulfides can be afforded in good yields using 5 mol % of Cu$_2$O and 10 mol % of 1,10-phenanthroline as the ligand. This work is indeed the first intermolecular copper-catalyzed coupling reaction of alkyl vinyl bromides with thiols. Synthesis of bioactive molecules by this method is currently in progress.

Table 4. Cu$_2$O-Catalyzed Coupling Reaction of Alkyl Vinyl Bromides and Chlorides with Thiols[a]



entry	X	product		yield (%)[b]
1	Br		**3d**	trace
2				93
3	Br		**3o**	99
4	Br		**3c**	90
5	Br		**3p**	trace
6	Br		**3b**	81
7	Br		**3r**	55
8	Br		**3e**	27[c]
9	Cl		**3k**	0[d]

[a] Reaction conditions for vinyl bromide: Cu$_2$O (0.025 mmol, 5 mol %), vinyl bromide (0.6 mmol), thiol (0.5 mmol), KOH (1 mmol), 1,10-phenanthroline (0.025 mmol, 10 mol %), in dioxane (0.25 mL). [b] Isolated yield. [c] 48 h. [d] Vinyl chloride (0.6 mmol) was used.

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Supporting Information Available. Experimental details and NMR spectra for compounds. This material is available free of charge via the Internet at http://pubs.acs.org.